

Physiological concept of hapten-carrier adduct vis-a-vis *Garavisha*

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Abstract

The human body defends itself from harmful agents such as microorganisms present in the environment, which otherwise damage the individual's health. This defensive mechanism is the immune response mediated by the activation of T-cell and B-cell antibody production. The body recognizes and destroys these antigenic harmful agents. The defensive response is altered sometimes in the presence of allergens, causing hypersensitive reactions. The allergens are antigens. The hapten-carrier adduct often behaves as an allergen-producing hypersensitivity with a manifestation of sign and symptoms those are at times lethal. *Garavisha* is an artificial type of poison formed by combination of two nonpoisonous substances as depicted in the treaties of Ayurveda. It has identical characteristics to that of hapten-carrier adduct. In the present article, *Garavisha* is substantiated with conceptual reference to hapten-carrier adduct and hypersensitivity.

Keywords: *Garavisha*, haptens, hypersensitivity, *Visha*

Introduction

Human body has the natural tendency to defend itself by eliciting immune response for the maintenance of health. Immune response is recognizing and destroying the antigens of microorganism by triggering the innate immune components such as activation of T-cell or production of antibodies. Sometimes in the sensitive individuals antigens present in the environment produces altered immune response called hypersensitivity. It is manifested with signs and symptoms that are at times lethal. Hapten-carrier adduct behaves as an allergen and induces hypersensitive reactions. Hapten is a small molecule which combines with a large protein, forming hapten-carrier adduct and evokes immune response. Signs and symptoms often with detrimental effect are also found when the body is afflicted with *Garavisha*. It is a type of *Kritrima Visha* (artificial type of poison) formed by the combination of two nonpoisonous substances. In the present study, *Garavisha* is substantiated with conceptual reference to hapten-carrier adduct and hypersensitivity.

Objectives

To substantiate the concept of hapten-carrier adduct and its hypersensitive response in the context of *Garavisha*.

- Concept of immune response: Immune response is the mechanism of host's immune system to eliminate foreign agents such as microorganisms efficiently and rapidly from the body. It is mediated by T- and B-lymphocyte based on specific antigen recognition, followed by triggering T-cell activation and B-cell antibody production and their simultaneous interaction with antigens^[1]
- Concept of antigen and allergen: Antigens that produce potent immunogenic response are large molecules with high molecular weight of 100,000 Dalton. Hapten is an antigen but cannot induce immunogenic response unless combine with large protein to form hapten-carrier adduct.^[2]

All allergens are antigens, but all antigens are not allergens. Allergens are substances causing harmful hypersensitive reaction. Allergen does not produce reaction in some people yet in others produces hypersensitive response. Some common allergens are pollen, dust, food, and drugs. Both allergen and

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antigen make up body's immune system to respond, but their effect is different. Immune response by antigen that is not allergen is just adequate and functions to maintain health, while allergen disturbs health in hypersensitive individual.

Concept of hapten-carrier adduct

Karl Landsteiner is the pioneer of the concept of hapten. Haptens are small molecules (<1000 D) that combine with large protein to form hapten-carrier adduct. Hapten alone cannot elicit immune response; even the carrier protein by itself may not produce the same. The hapten-protein combination is the hapten-carrier adduct that acts as antigen and binds with specific antibodies or activated T-cell to produce immune reaction. Hapten-carrier adduct some time acts as allergen and their exposure primarily occurs through skin surface, oral route, and respiratory tract. The dietary hapten exposure through processed food and formula milk is common nowadays.^[3] Notable example of hapten is urushiol which is absorbed through the skin and undergoes oxidation to produce a reactive molecule quinone (the actual hapten). Quinone reacts with skin protein to form hapten-carrier adduct which acts as toxin. The first exposure of the body to the hapten-carrier adduct causes sensitization and proliferation of the effect or T-cell, while in the subsequent exposure, the activated T-cell generates immune reaction by producing skin blisters.^[4]

Concept of hypersensitivity

Under normal circumstances, host defense in proper progressive order culminates in well-controlled immune and inflammatory response that protects him/her from offending antigens. The immune response in some person appears as side effect called hypersensitivity.^[5] Hypersensitivity is a symptomatic interaction between host defense and allergen causing exaggerated and harmful response in the body. Hypersensitivity is frequently known as allergy and reaction ranges from mild to life-threatening. It is mainly of two types, immediate hypersensitivity and delayed hypersensitivity.^[6] In immediate hypersensitivity reactions, there is immediate manifestation of symptoms and is mediated by IgE antibody. The antigen binds to IgE antibodies already attached to the mast cell because of previous exposure to the same antigen. The antigen-antibody reaction releases plenty of histamine and other chemicals from mast cell causing vasodilatation and shock along with other symptoms. Delayed hypersensitivity reaction is mediated by T_H 1 helper T-cells (T_4 cell). The reaction results in delayed symptoms. In the first exposure, allergen processed by the macrophage is presented to T_4 cell for its activation. In the second exposure, more activated T_4 cells are formed. T_4 cell secretes many chemicals causing activation of more macrophages that destroy the allergen and at the same time, there are indurations, redness and destruction of healthy tissues in that area. Antigen in the form of allergen introduced for the first time in life in host body is the sensitizing dose and reaction does not occur, but on second exposure, reactions appear.

In the traditional Gell and Coombs system of classification, hypersensitivity reactions are of four types:^[7]

- Type I hypersensitivity reaction is IgE antibody reaction. Atopic allergy with genetic predisposition belongs to this category
- Type II hypersensitivity reaction is cyto-toxic reaction
- Type III hypersensitivity reaction is immunocomplex reaction
- Type IV hypersensitivity reaction is delayed reaction mediated by helper T-cell.

The former classification of two types of hypersensitivity reaction (immediate and delayed) is relevant for the present article.

The concept of *Visha*

The word *Visha* is derived from the root “*Vis*” by having “*Ka*” preposition. This means to encompass, pervade, or occupy. The term *Visha* gets its name from *Vishada*. Substance that enters and vitiates the healthy *Dhatu* (structural components, tissues) of the body and may or may not manifest with lethal signs and symptoms is termed as *Visha*.^[8]

Ayurveda describes three varieties of *Visha*, i.e., *Jangama* (animal origin), *Sthavara* (plant and mineral origin) and *Kritrima* (artificial poison).^[9]

The third variety of poison is prepared by the combination of different materials. When it is produced by the combination of two nonpoisonous materials, it is called *Garavisha*; while combination of two poisonous materials forms *Kritrima Visha*.^[10]

The concept of *Garavisha*

The word *Gara* is derived from root word “*Gri*” with the suffix “*Ac*.” This means diluted or reduced in potencies.^[11] *Garavisha* is a combination of two nonpoisonous substances. It slowly produces toxic effect by vitiating the *Dhatu* (structural components of the body). This is followed by manifestation of mild to drastic clinical features. Unlike other poison, it does not cause instantaneous death. *Garavisha* commonly enters the body through food preparations.^[12] By nonpoisonous, it means that each ingredient forming *Garavisha* when enters the body separately does not produce any symptom, but their combination has poisonous effect producing adverse clinical features such as laziness, heaviness of the body, cough, dyspnea and edema that appear after 15 days or 1 month duration of affliction.^[13] There are ten attributes of *Visha*.^[14] These are equally applicable for *Garavisha* but are of *Alpa Virya* (mild intensities).^[15]

Concept of *Viruddha*

The literal meaning of word *Viruddha* is opposite. In the present context, it means substances producing incompatibility leading to toxic reaction in the tissues and exerting abnormal effects on the body.^[16]

Concept of *Viruddha Ahara*

Some food causes *Dosha Utklesha* (excited condition of humors) that is unable to eliminate from the body. They are called *Viruddha Ahara* (incompatible

food).^[17] Incompatible food arises in relation to *Desha* (habitat), *Kala* (time), *Anala* (agni), *Matra* (dose), *Satmya* (habit), *Dosha* (body humors), *Samskara* (mode of preparation), *Virya* (potency), *Koshtha* (condition of bowel), *Avastha* (condition of health), *Karma* (order), *Parihara* (proscription), *Upachara* (prescription), *Paka* (cooking), *Samyoga* (combination), *Hridya* (palatability), *Sampad* (richness of quality) and *Vidhi* (rules for eating).^[18] This disturbs the tissue metabolism causing abnormal reaction and undesirable effect in the body. *Viruddha Veerya* (incompatible potency) is important among the mentioned incompatibilities.

Concept of *Viruddha Veerya*

Substances such as drug and food manifest their actions by virtue of *Veerya* (potency). Some authors consider *Veerya* to be eight types while others consider two. *Veerya* of two types is popular and widely accepted in ancient treatises. *Sheeta Veerya* (cold potencies) and *Ushna Veerya* (hot potencies) are the two varieties of *Veeryas*.^[19] *Sheeta* and *Ushna* are not merely the temperature status but reactions of the substances in the body. Therefore, specificity of action of food and drugs are determined by *Sheeta* and *Ushna Veerya*. Combination of substances with two mutually contradictory potencies causes *Viruddha Veerya*. *Sheeta* and *Ushna* have their difference in the body that may not be harmful, but such mutual contradictory potencies combined together may be toxic and may render adverse resultant reaction in body.^[20]

Example of *Veerya Viruddha* (incompatible potency)

Consumption of fish with milk is an example of *Virya Viruddha* food. Milk and fish are two highly nutritious dietary substances when used separately, with rich in protein content. When used in combination, it produces undesirable side effect such as *Kushtha* (skin disorders).

Consequence of *Viruddha*

Viruddha Ahara^[21] plays a pivotal role in the development of *Tvaka Vikara* (skin disorders) along with the disturbance in different systems of the body.

The development of *Amadosha* is due to violation of the dietetic rule, that is, intake of diet that is *Atishita* (too cold) and *Atishushka* (too dry). Such substances cannot be properly digested. Protein food with the above qualities undergoes improper digestion and absorption. Partially digested protein when get absorbed acts as a carrier protein because of high molecular weight and on availability of a hapten, which combines with it to serve as allergen producing *Amadosha*. Regular indulgence in *Viruddha Ahara* induces inflammatory process by disturbing the eicosanoid pathway and increasing prostaglandin-2 and thromboxane level.^[22] *Agnimandya* and *Ama* formation are the results of this inflammatory effect.^[23]

Consumption of *Pathya* (wholesome) and *Apathya* (unwholesome) at the same time makes it unwholesome in totality. It acts like *Garavisha* showing delayed effect. The said combination of food induces slow inflammatory process, which in due course produces *Tvaka Vikara* such as *Visphota* (boils)

and *Vidradhi* (abscess).^[24] Consumption of food with opposite potencies such as milk with fish and milk with egg and food with opposite combination such as milk with banana and milk with mango are the etiology of *Kushtha* (skin lesion with varying systemic symptoms). These are apparently safe foods when consumed individually, but their combination produces delayed toxic interactions in the body such as hypersensitive reaction in the form of skin lesion and asthmatic attack.^[25,26]

The patho-physiological state in relation to *Viruddha Ahara* and *Viruddha Veerya* introduces allergens such as hapten-carrier adduct causing hypersensitivity by inflammatory process whose immediate effect is less significant but may precipitate serious side effects later on such as skin lesion and asthmatic attack.^[27]

Discussion

Garavisha is a combination of two nonpoisonous components (substances) producing signs and symptoms of *Visha* after application or consumption. Hapten-carrier adduct is also a combination of two components, hapten and carrier protein. As a single component hapten or carrier protein does not function as immunogen and cannot elicit immune response.

Single component of *Garavisha* also does not produce *Visha* (toxic) effect. They produce toxic effects on combination. The combining substances forming *Garavisha* may be of *Viruddha Veerya* (mutually contradictory potencies) obtained from *Viruddha Ahara* and other sources of *Viruddha*. The resultant reaction of two mutually contradictory potencies is adverse for the body and hence, *Garavisha* is a toxin and behaves as an allergen. The hapten and the carrier protein do not produce immunogenic effect separately, but their combination as hapten-carrier adduct makes them bind to the antigen presenting cell for activation of T- and B-cells and produce harmful immune reaction. Hence, *Garavisha* has a striking similarity with the hapten-carrier adduct.

Garavisha like other varieties of *Visha* causes *Vishada* or stressful condition. It is of slow reacting nature and gradually produces toxic effect by vitiating *Dhatu* through formation of *Amadosha* and *Agnimandya*, while exposure to hapten-carrier adduct causes sensitization and proliferation of the effector T-cells and antibodies present in the body, and on subsequent exposure, sometimes, stressful immune response is triggered at the site (tissues) of sensitization by activated memory T-cell and antibodies. The stressful immune response is the adverse effect of body's defensive mechanism and is called hypersensitivity. The reaction of *Garavisha* is likely comparable to hypersensitive response to body's immune mechanism.

In immediate hypersensitivity reaction, response is seen within 12 h of antigen challenge to preformed antibodies. Atopic allergy with genetic predisposition (allergy running in the family) produces immediate hypersensitive response with symptoms manifesting within few minutes to few hours.

Symptoms appear after 2–4 weeks due to *Garavisha* affliction. In Ayurvedic treaties, *Garavisha* poisoning is not included under *Kulaja Vyadhi*. Immediate hypersensitivity reaction along with atopic allergy does not match with the characteristic result of *Garavisha* and so cannot be included under its ambit.

Kalantara Vipaka^[28] implies delayed reaction of *Garavisha*. It takes time for such poison to get metabolized and produce toxic effect. This feature is common to delayed hypersensitivity reaction that takes few days to week for the development of symptoms. *Garavisha* is analogues to hapten-carrier adduct that can produce delayed hypersensitivity.

Conclusion

The concept of hapten-carrier adducts and delayed reaction hypersensitivity existed in the Ayurvedic treaties centuries ago and the terms *Garavisha* was applied for it. Clinically, hapten-carrier adduct and *Garavisha* produce more or less same type of clinical manifestation and systemic involvement. This aroused the necessity to relate *Garavisha* with hapten-carrier adduct. Further comprehensive and analytical studies are necessary to establish the concept of *Garavisha* with hapten and hapten-carrier adduct which may open new dimensions to understand the concept of *Garavisha*.

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Conflicts of interest

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References

- Haynes BF, Fauci AS. Disorders of the immune system. In: Eugene Braunwald, Anthony S. Fauci, Dennis L. Kasper, Stephen L. Hauser, Dan L. Longo, J. Larry Jameson, editors. Harrison's Principles of Internal Medicine. 15th ed. USA: The McGraw-Hill; 2001. p. 1805, 1825.
- Singha Mahapatra AB. The immune system. In: Essentials of Medical Physiology. 3rd ed. Kolkata: Current Book International; 2008. p. 45.
- Sicherer SH. Epidemiology of food allergy. J Allergy Clin Immunol 2011;127:594-602.
- Karl L. The Specificity of Serological Reaction. 2nd ed. New York: Courier Dover Publication; 1990. p. 205, 330.
- Chaudhury Sujit K. Concise Medical Physiology. 6th ed., Ch. 4. Kolkata: Central Book Agency (P) Ltd.; 2008. p. 63.
- Singha Mahapatra AB. The immune system. In: Essentials of Medical Physiology. 3rd ed. Kolkata: Current Book International; 2008. p. 52.
- Chaudhury Sujit K. Concise Medical Physiology. 6th ed. Ch. 4, Kolkata: Central Book Agency (P) Ltd.; 2008. p. 64.
- Namburi Sekhar UR. Introduction to Visha. In: A Text Book of Agad Tantra. 1st ed. Varanasi: Chowkhamba Sanskrita Bhawan; 2006. p. 6.
- Srikantha Murthy KR, editor. Sushruta Samhita of Acharya Sushruta, Kalpa Sthana. 1st ed. ch. 2, Ver. 24. Varanasi: Chaukhamba Orientalia; 2002. p. 423.
- Bhagwan D, Sharma RK, editor. Charaka Samhita of Acharya Charaka, Chikitsa Sthana, 6th ed. Ch. 23, Ver. 14. Varanasi: Chaukhamba Sanskrit Series; 1999. p. 326.
- Namburi Sekhar UR. Artificial poison (Garavisha). In: A Text Book of Agad Tantra. 1st ed. Varanasi: Chaukhamba Sanskrita Bhawan; 2006. p. 178.
- Bhagwan D, Sharma RK, editor. Charaka Samhita of Acharya Charaka, Chikitsa Sthana. 6th ed. Ch. 23, Ver. 233. Varanasi: Chaukhamba Sanskrit Series; 1999. p. 381.
- T Indradev, T Dayashankar. Yoga Ratnakara, Jangama Visha Chikitsa Adhaya. Varanasi: Krishnadas Academy; 1998. p. 866.
- Bhagwan D, Sharma RK, editor. Charaka Samhita of Acharya Charaka, Chikitsa Sthana. 6th ed. Ch. 23, Ver. 24-27. Varanasi: Chaukhamba Sanskrit Series; 1999. p. 330.
- Srikantha Murthy KR, editor. Astanga Hridayam of Acharya Vagbhata, Uttara Sthana. 1st ed. Ch. 35, Ver. 49. Varanasi: Krishnadas Academy; 1995. p. 336.
- Bhagwan D, Sharma RK, editor. Charaka Samhita of Acharya Charaka, Sutra Sthana. 6th ed. Ch. 26, Ver. 86-101. Varanasi: Chaukhamba Sanskrit Series; 1999. p. 484.
- Tumram AC, Chawre SV, Suryavanshi SS, Kamble MR, Sindel VS. Review on therapeutic significance of Viruddhahara (incompatible food combination). Int. J. Res. Ayurveda Pharm. 5 (4), Jul-Aug 2014:571.
- Bhagwan D, Sharma RK, editor. Charaka Samhita of Acharya Charaka, Sutra Sthana. 6th ed. Ch. 26, Ver. 64-65. Varanasi: Chaukhamba Sanskrit Series; 1999. p. 485-86.
- Bhagwan D, Sharma RK, editor. Charaka Samhita of Acharya Charaka, Sutra Sthana. 6th ed. Ch. 26, Ver. 64-65. Varanasi: Chaukhamba Sanskrit Series; 1999. p. 476.
- Bramhananda T, editor. Charaka Samhita of Acharya Charaka, Sutra Sthana. 5th ed. Ch. 26, Ver. 93. Varanasi: Chaukhamba Sanskrit Pratisthan; 1997. p. 497.
- Indra Kumar P. A Conceptual and Applied Study of Viruddha Ahara w.p.r. to Eka Kushtha. (Dissertation), Jamnagar, IPGT and RA; Gujarat Ayurveda University; 2003.
- Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. ArteriosclerThrombVascBiol2011;31:986-1000.
- Sabnis M, Ahara V. A critical review. AYU 2012;33:332-6.
- Vaidya Asmita. A Critical Study of Hitahitiya Adhyaya of Sushruta Samhita w.s.r.to Viruddha Ahara: An Experimental & Survey Study. (Dissertation), Jamnagar, IPGT and RA; Gujarat Ayurveda University; 2012.
- Katta R, Schlichte M. Diet and dermatitis: Food triggers. J ClinAesthetDermatol2014;7:30-6.
- Wang J, Liu Andrew H. Food allergies and asthma. Current Opinion in Allergy and Clinical Immunology. 2011;11:249-54.
- Liu ZQ, Zheng PY, Yang PC. Hapten facilitates food allergen-related intestinal hypersensitivity. Am J Med Sci 2013;345:375-9.
- Bhagwan D, Sharma RK, editor. Charaka Samhita of Acharya Charaka, Chikitsa Sthana. 6th ed. Ch. 23, Ver. 14, Varanasi: Chaukhamba Sanskrit Series; 1999. p. 326.